Comparative Effectiveness of Different Antiplatelet Regimens in Patients with Acute Coronary Syndrome: A Systematic Review

Abstract

Acute coronary syndrome (ACS) has been a leading cause of mortality and mortality. Platelet accumulation plays a vital role in the development and pathogenesis of ACS, making antiplatelet therapy a keystone in their inhibition and control. The purpose of this review is to highlight the effectiveness of different antiplatelet therapies in ACS patients. The methodology followed in this review is Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. 38 studies included in this review from the past 10 years. Google Scholar and PUBMED were used for collecting articles. Findings pointed out that traditional antiplatelet agents such as aspirin and clopidogrel have been used for a long time in treating ACS patients. Regardless of their benefits limitation included slow speed of onset, weak efficacy, and low antiplatelet effect. These limitations were overcome by recently developed novel antiplatelet agents such as rivaroxaban, ticagrelor, and prasugrel as offering more strong and expectable platelet inhibition and showing a significant reduction in stent thrombosis, major adverse cardiac or cerebral events MACCE, low mortality rate in patients with ACS but at the expense of increased risk of heavy bleeding in some cases. Another strategy that involves the combination of different antiplatelet therapies known as dual antiplatelet therapy also resulted in more safety and effectiveness while treating ACS patients. In conclusion, the effectiveness of antiplatelet treatments depends on the individual patient's characteristics and risk factors. However, maintaining the correct balance between reducing the risk of heavy bleeding and major cardiovascular events remains a crucial challenge. Further research needed to be done to improve our strategies in treating ACS patients.

Introduction

Acute coronary syndrome (ACS) includes wide range of clinical conditions like myocardial ischemia, unstable Angina, non-ST segmented elevation myocardial infarction (NSTEMI) and ST-segmented elevation myocardial infarction (STEMI)(Dawwas et al., 2019). ACS mostly initiates by intracoronary thrombus formation and atherosclerotic plaque rupture(Roe et al.,

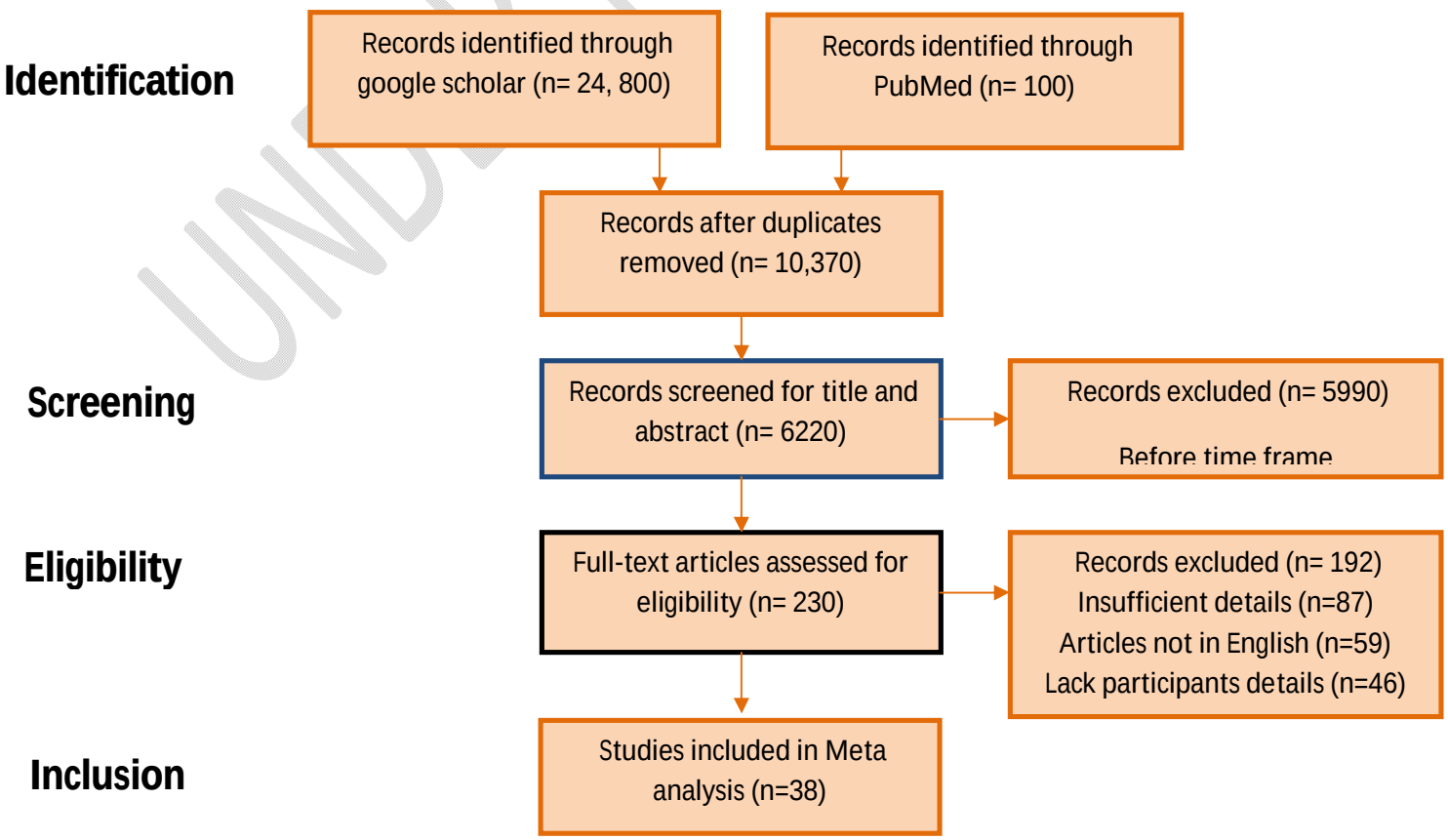
2000). ACS ranges from complex ulcerated lesion to insignificant coronary artery diseases that occur in 15-20% of patients who undergo angiography(Libby, 1995). 7 million people die each year due to Acute coronary diseases and acute coronary artery syndrome collectively(Sharma, Kumar, Prashanth, Belagali, & therapy, 2020). Electrocardiography ECG was initially used for the treatment of coronary artery diseases and now clinical advances include coronary endarterectomy, coronary artery bypass grafting, percutaneous coronary intervention PCI and antiplatelet therapies(Libby, 1995).

ACS is mainly driven by platelet aggregation. Multiple dual and single antiplatelet therapies with different antiplatelet combinations are used to treat ACS. Dual antiplatelet therapies include combination of Aspirin with any other $P2Y_{12}$inhibitors like clopidogrel, ticagrelor and prasugrel. DAPT therapy is superior and more effective than SAPT(Sharma et al., 2020). DAPT therapies reduces the major ischemic events in ACS patients but DAPT therapy is associated with major bleeding events(Nguyen et al., 2007).In Single Antiplatelet therapy and Dual antiplatelet therapies patients are treated with oral $P2Y_{12}$ receptor antagonists like aspirin, clopidogrel, ticagrelor and Prasugrel. These $P2Y_{12}$ receptor antagonists prevent thrombotic complications in ACS or PCI(Franchi et al., 2019). Aspirin is adenosine purinergic (ADP) receptor P2Y12 inhibitors. The high intensity platelet inhibition is by simultaneous blockage of COX cyclooxygenaseand ADP dependent pathways. This high antithrombotic effect of aspirin increases bleeding complications(Passacquale, Sharma, Perera, & Ferro, 2022). Antiplatelet clopidogrel is inactive thienopyridine drug that is initially metabolized in liver and converted into active metabolites that selectively and irreversibly inhibits adenosine 5′-diphosphate (ADP)–induced platelet aggregation(AlMukdad, Elewa, Al-Badriyeh, & therapeutics, 2020). Clinical studies have shown that 16-50% of patients have clopidogrel resistance which means these patients are still at the risk of adverse cardiovascular events even after taking standard dose of clopidogrel(Qian et al., 2022). Ticagrelor is cyclo-pentyl triazole pyrimidines having fast, strong and reversible inhibitory effect on platelet activation and aggregation(Qian et al., 2022). Prasugrel is $P2Y_{12}$ receptor antagonists inhibits platelet activation and aggregation stronger and faster(Dawwas et al., 2019). Prasugrel antiplatelet is also affected by *CYP2C19* gene polymorphism and currently it is ban in China(Qian et al., 2022).

Methodology

We systematically reviewed the experimental and epidemiological studies of last 10 years (2013-2023) to study the comparative effectiveness of different antiplatelet on acute coronary artery syndrome on multiple electronic databases like Google Scholar and PubMed. The key words like "*Acute Coronary syndrome/ ACS*", "*Comparative effectiveness of Antiplatelet*", "*Dual antiplatelet therapy/ DAPT*", "*Single antiplatelet therapy/ SAPT*", "*Ticagrelor*", "*clopidogrel*"and "*prasugrel*"were used to retrieve the relevant studies. After carful screening 5669 duplicate articles were excluded. All the articles out of timeline were neglected. 260 articles were excluded due to insufficient details, non-original research, different language, and lack of proper evidence. We didn't omit any article based on negative or positive findings. Finally,40 articles were reviewed following the 2020 Preferred Reporting Items for Systematic Review and Meta Analysis Protocols (PRISMA) statement.

Fig 1. PRISMA Flowchart



Results And Discussion:

Mono Antiplatelet Therapy:

1. **Cilostazol**

A study conducted on ACS patients to observe the Efficacy and safety of individually tailored antiplatelet therapy. Patients with low responsiveness to clopidogrel get treated with additional cilostazol for six months. Results showed a reduction in cardiovascular deaths, hearth attacks and strokes compared to the standard group. But further studies are required (Zhu et al., 2015).

2. **Aspirin**

To prove aspirin desensitization is an effective and safe treatment for ACS patients a study was conducted on 24 ACS patients with aspirin hypersensitivity history. All the patients were treated successfully with aspirin desensitization protocol, only one patient showed urticarial reaction. Of all the patients, 5 patients with ST segment elevation myocardial infarction were given abciximab until desensitization was completed. All patients underwent catheterization and upon follow up only 2 patients stopped taking aspirin because of gastrointestinal bleeding, with no hypersensitivity reactions reported proving the safety and effectiveness of aspirin desensitization in ACS patients both long and short term(Córdoba-Soriano et al., 2016).

3. **Bivalirudin**

A study was conducted in ACS patients undergoing PCI to compare different treatment approaches: bivalirudin with restricted use of glycoprotein IIb/IIIa inhibitors and heparin with or without glycoprotein IIb/IIIa inhibitor. The findings showed that bivalirudin alone did not results in the reduction of MACE and bleeding events in patients with or without ST segment elevation in ACS. (Leonardi et al., 2016).

4. **Methyltrexone**

A study was conducted on American coronary artery disease patients revealed that morphine used for pain relief purposes delays the effect of $P2Y_{12}$ receptors including ticagrelor by rapid gastric emptying. Now methyl-trexone is peripheral opioid receptor antagonists delays gastric emptying and enhance gastrointestinal absorption without effecting platelet activity(Franchi et al., 2019).

5. Tirofiban

A cohort study was conducted on 104 progressive ischemic stroke patients to evaluate the effectiveness and efficacy of Tirofiban in combination with DAPT. After 14 days follow-up the health stroke scale score of tirofiban group was significantly lower. After 90 days excellent health outcomes were observed in tirofiban cohort proving superiority of tirofiban on DAPT(Zhang et al., 2021).

6. Apixaban

The author reported that when high risk of ACS patients already taking aspirin alone and aspirin plus clopidogrel were randomized to receive apixaban or placebo. No significant association was observed as it did not affect the composite endpoint of cardiovascular death, myocardial infraction and ischemic stroke in patients receiving aspirin and aspirin plus clopidogrel. However, both groups receiving apixaban showed increased risk of thrombolysis in myocardial infraction major bleeding. This suggests that post ACS treatment with apixaban is not efficient and has an increased risk of bleeding(Hess et al., 2015)

7. Rivaroxaban

Three studies were conducted to examine which dose of rivaroxaban 2.5 mg or 5mg is more effective. Author conducted a study to observe the safety and efficacy of rivaroxaban in patients with ST-elevation myocardial infarction (STEMI). Findings showed that rivaroxaban 2.5 mg dose reduced the primary endpoint of cardiovascular events like stroke and heart attacks when compared with placebo while no benefit was observed at 5mg of dose. However, treatment with rivaroxaban showed an increased risk of bleeding but not enough to cause death(Mega, Braunwald, Murphy, et al., 2013).Similarly, the author reported that patients treated with 2.5 mg dose twice daily of rivaroxaban showed a significant reduction in stent thrombosis, low mortality rate in patients with ACS(Gibson et al., 2013). Another study backing up the above studies stated that no significant difference was observed between two doses and MACE while 2.5mg results in fewer bleeding complications and fewer drug discontinuation making is safer and more efficient than 5mg dose(Mega, Braunwald, Wiviott, et al., 2013).

ComparisonBetween Different SAPT

1. **Antiplatelet Clopidogrel Vs Ticagrelor:**

Out of 40 studies, 7 studies were conducted to observe the efficacy and safety of clopidogrel vs ticagrelor. Four studies reveal ticagrelor is more effective than clopidogrel in ACS patients. The author reported that when ticagrelor, a direct- acting inhibitor of P2Y12 and clopidogrel were compared in patients with acute coronary syndrome. Ticagrelor showed significant benefits over clopidogrel as it reduced in-stent thrombosis and helped in reduction of target vessel revascularization (TVR). However, it was associated with a higher rate of minor bleeding and there was no significant difference in major adverse cardiovascular and cerebrovascular events (MACCE) between the groups(Xin et al., 2017). Another study demonstrated that ticagrelor showed more dominance over clopidogrel in reducing ischemic events at the cost of increased risk of non-fatal bleeding. Further investigation was done to examine whether this held true for Asian people as they are more prone to bleeding. Results showed that the effects of ticagrelor versus clopidogrel were constant as no significant signification difference was observed in efficacy outcomes, net clinical outcomes between both Asian and non-Asian ACS patient groups(Kang et al., 2015). Similarly,A cohort study was conducted on 3528 Chinese ACS patients in 2023 demonstrated that the incidence of major adverse cardiovascular events, incidence of all cause deaths and cardiovascular deaths were significantly lower in ticagrelor than clopidogrel groups. While there was no significant difference between recurrent myocardial infarction, repeated revascularization, major and minor bleeding events in both groups(Wu & Jia, 2023). A cohort study was conducted in 2022 on 170 ACS patients reveals that patients with CYP2C19 loss of function allele are at significantly higher risk of stent thrombosis and angina symptoms. Coronary artery patients having single LOF allele taking ticagrelor have better prognosis than clopidogrel. While the patients having two LOF allele taking ticagrelor showed no clinical benefits compared to the patients taking clopidogrel(Qian et al., 2022).

But the result of two studies showed that ticagrelor is associated with more bleeding events than clopidogrel. A study conducted on ACS Chinese patients who underwent PCI showed that patients receiving ticagrelor have the same risk of net adverse clinical events when compared to those on clopidogrel. However, ticagrelor increases major adverse cardiac or cerebral events (MACCE) in patients with high to moderate bleeding potentials while reduces MACCE in

patients with low bleeding risk. These results suggest that ticagrelor has efficacy and safety in patients with low potential of bleeding risk but not in patients with higher bleeding risk(Wang, Li, Xu, Li, & Han, 2018). Similarly,A cohort study conducted in 2020 on 137 ACS patients to compare the effectiveness of DAPT aspirin-clopidogrel and aspirin-ticagrelor after coronary endarterectomy CE and coronary artery bypass grafting CABG. This study reveals that DAPT are effective after CE+CABG. But ticagrelor was associated with more bleeding events than clopidogrel while no significant differences was observed in MACCE events(Yan, Tiemuerniyazi, Song, Xu, & Feng, 2020).

A cohort study was conducted on Chinese coronary artery disease patients undergoing percutaneous coronary intervention demonstrated that antiplatelet ticagrelor was cost effective compared with clopidogrel. The analysis showed that ticagrelor use was cost–effective for an ICER of 33,875 yuan per QALY gained compared with 'universal clopidogrel use' of which gained a 1.6932 QALYs at lowest life-long cost of 2450 yuan.

2. **Antiplatelet ticagrelor vs prasugrel**

Three studies were conducted to compare the effectiveness of ticagrelor vs prasugrel in ACS patients. Two studies showed that ticagrelor has more benefits over prasugrel. As author reported that ticagrelor has more benefits then prasugrel as it has more consistent positive results, pretreatment potential and reduced cardiovascular events while in contrast prasugrel showing increased bleeding risk with pretreatment(Schulz et al., 2014). Similarly In 2019 a cohort study was conducted on 29714 ACS patients reveals that risk of major bleeding events and recurrent nonfatal CVD events were significantly lower in ticagrelor group compared to the prasugrel group(Dawwas et al., 2019). While another study contradicting the first two studies observed the effectiveness of two antiplatelet ticagrelor and prasugrel in East Asian patients with ACS. Patients in three groups were given 90 mg of ticagrelor twice daily, 5mg of prasugrel daily and 10 mg of prasugrel daily. After analyzing platelet reactivity 5 mg prasugrel groups showed highest reactivity followed by 10 mg of prasugrel and ticagrelor groups. Suggesting 5 mg must be the best choice for ACS patients of East Asian patients(J. H. Lee et al., 2015).

3. **Antiplatelet Clopidogrel and prasugrel**

While comparing clopidogrel and prasugrel two studies showed that prasugrel was more dominant than clopidogrel as reported by author that switching to prasugrel from clopidogrel has reduced the P2Y12 reaction unit (PRU) values, tighter control to platelet activity and significant reduction in the occurrences of MACE; TIMI major bleeding accompanied by acceptable TIMI minor and non-major, non-minor clinically relevant bleeding in Chinese patients(Liu et al., 2022). Similarly, the impact of cytochrome P450 2C19 (CYP2C19) genetic variations on the safety and efficacy of clopidogrel and prasugrel was investigated in a post hoc analysis of the PRASFIT-ACS study involving Japanese patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). Patients that were randomized to receive clopidogrel and prasugrel combined with aspirin were classified into extensive metabolizers(D Alexopoulos et al.), intermediate metabolizers (IM), and poor metabolizers (PM) based on CYP2C19 genotypes by pharmacogenomic analysis. Irrespective of genotype, prasugrel showed lower platelet reactivity as compared to clopidogrel. IM + PM patients showed a trend towards lower major adverse cardiovascular events MACE rates with prasugrel, but no significant different association was observed in MACE between prasugrel and clopidogrel in EM patients. Overall, prasugrel demonstrated more consistent antiplatelet effects than clopidogrel in Japanese ACS patients, regardless of their CYP2C19 phenotype(Ogawa et al., 2016). However, Author reported that study was conducted to assess the safety and efficacy of early de-escalation to clopidogrel guided by platelet function testing (PFT) after an initial period of prasugrel. The primary end points including cardiovascular events and bleeding events showed net clinical benefits. The results showed that de-escalation of antiplatelet treatment was not less than the standard treatment with prasugrel. This indicates that using this de-escalation approach can be considered in ACS patients managed with PCI(Sibbing et al., 2017).

4. Antiplatelet Prasugrel Vs Aspirin

A study was conducted to compare the effectiveness of prasugrel, and aspirin reveals that when Japanese patients were treated with prasugrel (20/3.75mg) and aspirin combination 23% reduction was observed in risk of major adverse cardiovascular events (MACE) and serious clinical bleeding when compared with clopidogrel (300/75 mg) and aspirin combination indicating prasugrel at 20/3.75mg dose is effective and safe for Japanese ACS patients(Saito et al., 2014).

5. Combinations Of Clopidogrel, Prasugrel, And Ticagrelor

Two studies were performed to study the combination of clopidogrel, prasugrel, and ticagrelor. A study was conducted to observe the in hospital switching of P2Y122 inhibitors in ACS patients undergoing PCI. Switching occurred with various combinations of clopidogrel, prasugrel, and ticagrelor. Findings showed that when switching was done from clopidogrel to novel agent versus continuous novel agent administration no significant difference was observed in MACE or bleeding events but switching from clopidogrel to novel agent versus only clopidogrel administration shows more bleeding events but low MACE. Indicating in hospital switching is common in ACS patients but switching to a novel agent can be linked to an increased risk of bleeding(Dimitrios Alexopoulos et al., 2014). Similarly, the efficacy and safety of antiplatelet agents clopidogrel, prasugrel, and ticagrelor was investigated in ACS patients treated with PCI. Ticagrelor demonstrated no significant difference from clopidogrel in major adverse cardiovascular events (MACE) while prasugrel showed a lower rate of MACE compared to clopidogrel. However, both ticagrelor and prasugrel were associated with higher bleeding events as compared to clopidogrel. Overall, prasugrel was more efficient and safer but this advantage was balanced by a higher bleeding risk when compared to clopidogrel(D Alexopoulos et al., 2016).

6. Association OfPatients Genetic Makeup and Clopidogrel

Two studies were conducted to observe the association between genetic makeup and clopidogrel antiplatelet therapy. A study was conducted to look at CYP2C19 and ABCB1 genes of ACS patients that how these genes can affect the function of body processing clopidogrel. Results showed that patients with certain genetic variations and poor metabolism are more likely to have blood clotting issues, while those with ultra-rapid metabolism showed risk of high bleeding. So, it was suggested that ACS patients having genetic variations should be given another drug then clopidogrel(Galeazzi et al., 2018). Another study in 2020 was conducted in china on 2,000,000 ACS with PCI demonstrated that genome guided escalation of antiplatelet clopidogrel and ticagrelor is more effective than non-guided de-escalation(Limdi et al., 2020).

7. AssociationBetween Type II Diabetes and Clopidogrel Antiplatelet

A cohort study was conducted on 185 coronary artery patients including 58 diabetic patients to evaluate the association between type II diabetes and antiplatelet reactivity. This study reveals the positive association of type II diabetes with clopidogrel resistance. Diabetes, hypertension, hyperglycemia and obesity weakens the antiplatelet activity(Jastrzebska et al., 2019).

Findings of the above studies are also presented in tabular form in table 1.

DAPT vs SAPT:

Seven studies were conducted to study the effectiveness of DAPT vs mono antiplatelet therapy. Out of seven, five studies supported that DAPT is more effective. A cohort study conducted on Korean coronary artery disease patients in 2020 reveals that clopidogrel-aspirin DAPT is more effective and safer than aspirin monotherapy. There is significantly lower risk of all type of strokes like ischemic stroke and non-fatal stroke and all-causemortality in DAPT than aspirin monotherapy(H.-L. Lee et al., 2020). Another study conducted to check whether taking DAPT for 6 months is as good as taking it for 1 year a study was conducted on Korean people. The results showed that taking DAPT for 6 months is not bad as taking it for 1 year. But the group taking DAPT for 6 months showed slightly higher risk of having heart attacks, but it is not clear yet. So, it is suggested that ACS patients should keep taking DAPT for long time unless there is a high risk of bleeding(Hahn et al., 2018). Similarly, in 2022, a cohort study was conducted on 12 234 Korean ACS patients reveals that the risk of primary composite vascular events and recurrent strokes is significantly lower in clopidogrel-aspirin DAPT than other combined antiplatelet treatments. While there was no significant difference between aspirin monotherapy and combined antiplatelet therapies(S. Kim et al., 2022). A cohort study conducted in 2020 on 137 ACS patients to compare the effectiveness of DAPT aspirin-clopidogrel and aspirin-ticagrelor after coronary endarterectomy and coronary artery bypass grafting. This study reveals that DAPT are effective after CE+CABG. But ticagrelor was associated with more bleeding events than clopidogrel while no significant differences was observed in MACCE events(Yan et al., 2020). In 2019 a cohort study was conducted on 5590 Korean ACS patients. This 3 months follow-up study reveals that all type vascular events and recurrent strokes were significantly lower in patients treated with clopidogrel-aspirin DAPT than aspirin monotherapy(J.-T. Kim et al., 2019).

Two studies support SAPT. In 2021, A cohort study was conducted on European ACS patients reveals that DAPT is associated with more than dual risk of MACE than SEPT. More bleeding events occurred in patients with DAPT revealing that SAPT is safer than DAPT(Cerrato et al., 2021). Similarly, in 2019, a cohort study was conducted on 7585 patients undergoing PCI and 1-month DAPT followed by 23-month ticagrelor monotherapy and 12 months aspirin monotherapy. This study reveals that ticagrelor monotherapy protects from nonfatal myocardial infraction, nonfatal strokes, urgent TVR at 2 years and all causes of deaths. Moreover it reduces the risk of bleeding events than conventional aspirin monotherapy(Franzone et al., 2019).

One cohort study conducted in 2023 showed no significant difference between DAPT and SAPT. 671 patients were given DAPT for 1 year were switched to SEPT either aspirin or clopidogrel and followed for 4 years do not show any significant difference in overall mortality, major adverse events, acute myocardial infarction, ischemic stroke, coronary reintervention and major bleeding events. (J. S. Kim, Kang, Sohn, & Hwang, 2023).

Personalized Antiplatelet Therapy

In 2020, a cohort study was conducted on 2237 Chinese ACS patients undergoing PCI to evaluate the effectiveness of personalized antiplatelet therapy reveals that incidence of stent thrombosis, major adverse cardiovascular events (MACE) and major adverse cardiovascular and cerebrovascular events (MACCEs) were significantly lower in personalized antiplatelet therapy group. But no significant difference was observed in incidence of strokes, all-cause death, MI, major bleeding events and urgent revascularization.

Table1 Different antiplatelets effectiveness in different ethnic groups.

Sr no	Study type	Year	Ethnicity	Population	Antibiotics	More Effective
1	Cohort	2021	Japanese	203	Prasugrel vs clopidogrel	Prasugrel
2	Cohort	2023	Chinese	3528	Ticagrelor vs clopidogrel	Ticagrelor
3	Cohort	2020	Korean	15430	Clopidogrel-Aspirin vs	Clopidogrel-Aspirin

					Aspirin	
4	Cohort	2022	??	170	Clopidogrel vs ticagrelor	Clopidogrel
5	Cohort	2019	Korean	5990	Clopidogrel-aspirin vs aspirin	Clopidogrel-aspirin
6	Cohort	2019	9 countries	7585	DAPT vs ticagrelor	DAPT
7	Cohort	2019		29714	Ticagrelor vs prasugrel	Ticagrelor
8	Cohort	2015	Asian and non-Asian patients	Asian (n = 1,106) and non-Asian (n = 17,515) patients	Ticagrelor vs clopidogrel	Ticagrelor
9	Cohort	2015	Asia/Pacific, Eastern Europe, North and South America and Western Europe	7392	Apixaban	Treatment with apixaban is not efficient.
10	Randomized, double-blind, placebo-controlled	2013	North South America, Western Eastern Europe, Asia Pacific,	15,526	Rivaroxaban	Rivaroxaban

			and Others			
11	Randomized controlled trial.	2016	Italy, the Netherlands, Spain, and Sweden.	7213	Bivalirudin	Bivalirudin alone did not results in the reduction of MACE
12	Cohort	2018	south Korea	2712	aspirin plus a P2Y12 inhibitor	Taking aspirin plus a P2Y12 inhibitor for 1 year is effective.

Conclusion:

In conclusion, antiplatelet therapies help in the inhibition of blood clot formation further helping in prevention of MACCE in ACS patients. The comparative effectiveness of different antiplatelet therapies has different results and outcomes depending on individual patients' ethnic backgrounds and different characteristics, demonstrating not all patients respond the same way to these therapies.Different factors such as metabolism rate, genetic variations, and other health conditions play a major role in determining which therapy is safer and more effective for a specific individual. Findings also demonstrated that different ethnic groups have different metabolic rates for a specific drug modifying their overall efficacy. So different personalized medicines should be made for each patient with different traits and genetic makeup to reduce major cardiac events in patients with ACS. Further research is needed to better understand how tailored treatments will help us assist our patients.

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